Antifungal treatment for invasive Candida infections: a mixed treatment comparison meta-analysis


CRD summary
This review evaluated antifungal therapy on infection response rates, mortality and safety in adults with confirmed systemic fungal infection. The authors concluded that azoles and echinocandins were equally effective for treating invasive candidiasis and similar within-class effects were evident. Due to unclear study quality and concerns about the chosen method of synthesis, the reliability of these conclusions is unclear.

Authors' objectives
To evaluate the effects of antifungal therapy on infection response rates, mortality and safety in adults with confirmed systemic fungal infection.

Searching
MEDLINE, EMBASE, Cochrane Central Database of Controlled Trials (CENTRAL), AMED, CINAHL, TOXNET, Development and Reproductive Toxicology, Hazardous Substances Data Bank, PsycINFO, Web of Science and other databases that included full-text journals were searched from inception to May 2009. Search terms were reported. Bibliographies of systematic reviews and retrieved papers were searched for additional studies, including unpublished material.

Study selection
Randomised controlled trials (RCTs) that compared different antifungal treatments for patients aged at least 18 years with confirmed invasive candidiasis were eligible for inclusion in the review. The primary outcome of interest was clinical response rate. Secondary outcomes of interest were all-cause mortality, fungal-attributable death and adverse events. Trials were excluded if they reported only on dose-comparison or dosage form, single-site fungal infections and aspergillosis, cryptococcosis and endemic mycoses.

Most included trials compared azole-class drugs to amphotericin B. The included azoles were fluconazole, itraconazole and voriconazole. Other trials assessed echinocandins (anidulafungin, micafungin and caspofungin). Patients were mostly those with hematologic cancers infected with candida species. Mixed clinical populations were included. Median participant age was 57 years. Dosage, timing and definitions of response varied across included trials.

Two independent reviewers selected trials for inclusion in the review.

Assessment of study quality
Trial quality was assessed on allocation sequence generation, allocation concealment, blinding, loss to follow-up and intention-to-treat analysis.

Two reviewers independently performed quality assessment. Disagreements were resolved by consensus.

Data extraction
Data were extracted on numbers of events to enable calculation of relative risks (RR) and 95% confidence intervals (CI). Data were collected on posterior means and 95% credible intervals to enable the calculation of odds ratios (OR) in the mixed-treatment comparison analysis. Authors were contacted for clarification of data, where necessary.

Two independent reviewers performed data extraction.

Methods of synthesis
The analysis was twofold. For the analysis of study outcomes across classes of drugs (azole interventions versus all amphotericin B), relative risks and 95% CIs were pooled in a fixed-effect meta-analysis. Where there were zero events in one arm of a trial, the Haldane method was used and 0.5 was added to each arm. Multivariate meta-regression (amphotericin delivery and allocation concealment as covariates) was applied to assess the impact of individual azoles and delivery methods of amphotericin B on the overall estimates. The $I^2$ statistic was used to assess statistical heterogeneity. The relative effectiveness of each drug was evaluated by combining direct and indirect evidence in a fixed-effect analysis of mixed-treatment comparisons using a Bayesian approach that reported posterior means and 95% credible intervals.

**Results of the review**

Eleven RCTs ($n=965$) were included in the review. Overall trial quality was considered to be moderate; individual quality assessment results were not reported.

For global clinical response, a statistically significant pooled effect was found for azoles versus amphotericin B (RR 0.87, 95% CI 0.78 to 0.96, $I^2$=43%; seven trials). Similar effect estimates were reported when fluconazole (five trials), itraconazole (one trial) and voriconazole (one trial) were compared with amphotericin B; only the first of these analyses was statistically significant. Results for anidulafungin compared with fluconazole were also statistically significant (RR 1.26 95% CI 1.06 to 1.51; one trial).

For all-cause mortality, there was no statistically significant effect in the comparison of azoles versus amphotericin B. Similar results were reported for fluconazole (five trials), itraconazole (one trial) and voriconazole (one trial). There were no statistically significant effects in any of the analyses of micafungin versus caspofungin and anidulafungin versus fluconazole.

There were no statistically significant associations for deaths attributable to fungal infection.

Azoles were found to be favourable to amphotericin B in terms of a lower incidence of serious adverse events (RR 0.67, 95% CI 0.55 to 0.81; two trials). Echinocandins were similarly favourable to amphotericin B (RR 0.49, 95% CI 0.37 to 0.66; two trials). Micafungin and caspofungin had similar safety profiles. Azoles were favourable to amphotericin B on nephrotoxicity (RR 0.22, 95% CI 0.15 to 0.32; $I^2$=74%), as were echinocandins (RR 0.31, 95% CI 0.17 to 0.57). The only statistically significant result for hepatic enzyme elevations was in favour of anidulafungin over fluconazole (RR 0.21, 95% CI 0.05 to 0.83).

Mixed-treatment comparison analysis showed that within-class effects were similar across all drug interventions. Absolute response rates ranged from 63% (fluconazole) to 77.49% (anidulafungin). Absolute treatment efficacy in terms of mortality ranged from 20.75% (anidulafungin) to 39.99% (amphotericin B liposomal).

Sensitivity analysis on the dose of amphotericin B did not alter the main results.

**Authors’ conclusions**

Azoles and echinocandins were equally effective for treating invasive candidiasis and similar within-class effects were evident. Amphotericin B was an effective alternative, but was more toxic.

**CRD commentary**

The review question was clear and supported by detailed and potentially reproducible inclusion criteria. A number of general and specific data sources were searched. Attempts were made to minimise language and publication biases. The review process was conducted with sufficient attempts to minimise error and bias. Appropriate quality assessment criteria were applied to the RCTs. The results of this were not reported, which made it difficult to interpret the reliability of the included trials. Study details and statistical analysis indicated some degree of heterogeneity. Therefore, the choice of fixed-effects meta-analysis may not have been appropriate. The authors' conclusion broadly reflected the evidence presented, but due to a lack of clarity regarding trial quality and concerns about the chosen method of synthesis, the reliability of these conclusions is unclear.

The authors acknowledged various competing interests in terms of their connections with drug manufacturers.
Implications of the review for practice and research

**Practice:** The authors stated that this review confirmed the guidelines from the Infectious Disease Society of America, which recommended azoles or echinocandins as the first-line treatment for candida infections.

**Research:** The authors stated that future research should aim for more consistency in endpoint definitions to facilitate comparisons across trials.

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